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Clinical Article

Effect of Vagus Nerve Stimulation in Post-Traumatic Epilepsy and Failed Epilepsy Surgery : Preliminary Report

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Objective : Vagus nerve stimulation (VNS) has been used in epilepsy patients refractory to standard medical treatments and unsuitable candidates for resective or disconnective surgery. In this study, we investigated the efficacy of VNS to patients who had refractory result to epilepsy surgery and patients with post-traumatic epilepsy.
Methods : We analyzed the effect of VNS in 11 patients who had undergone previous epilepsy surgery and patients with intractable post-traumatic epilepsy associated with brain injury. All patients underwent VNS implantation between October 2005 and December 2006.
Results : We evaluated seizure frequency before and after implantation of VNS and maximum follow up period was 24 months. In the first 6 months, 11 patients showed an average of 74.3% seizure reduction. After 12 months, 10 patients showed 85.2% seizure reduction. Eighteen months after implantation, 9 patients showed 92.4% seizure reduction and 7 patients showed 97.2% seizure reduction after 24 months. Six patients were seizure-free at this time.
Conclusion : We conclude that the VNS is a helpful treatment modality in patients with surgically refractory epilepsy and in patients with post-traumatic epilepsy due to severe brain injury.

KEY WORDS : Vagus nerve · Electric stimulation · Epilepsy · Post-traumatic.

INTRODUCTION

Vagus nerve stimulation (VNS) has been used in epilepsy patients refractory to standard medical treatments, and who are unsuitable candidates for resective or disconnective surgery. Many authors have described the safety and effectiveness of VNS. Its benefits include reduction in the severity of seizures[9,10]. Several studies have shown that the effectiveness of VNS increases with time after the procedure[7]. However, most reports describe outcomes in intractable epilepsy patients who did not have epilepsy surgery. Moreover, the aforementioned data are from Caucasian patients. We analyzed the efficacy of VNS in intractable epilepsy patients who have undergone previous epilepsy surgery with unsuccessful results and in patients with posttraumatic epilepsy associated with severe brain injury.

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MATERIALS AND METHODS

Between October 2005 and December 2006, 11 patients with intractable epilepsy underwent VNS implantation and their outcomes were analyzed. Nine patients had undergone previous epilepsy surgery. These patients were not controlled from seizures on two or more anti-epileptic drugs despite surgical treatment. Two patients had post-traumatic epilepsy secondary to severe brain injury. Before VNS was performed, brain MRI, EEG, semiology, and type of previous epilepsy surgery were analyzed. VNS electrodes were implanted onto the left vagus nerve trunk below the superior and inferior cardiac branches. Pulse generator testing was performed for 30 seconds, initially at 0.25 mA output current, 30 Hz frequency, and 500 μs pulse width. Postoperative output current was escalated to 0.25 mA for every 4 weeks with 30 Hz frequency, 500 μs pulse width, 30-second on-time and 5-minute off-time. Postoperatively, we analyzed parameters (output current, frequency, pulse

width, and ON/OFF times) as well as seizure frequency and severity every 6 months.

RESULTS

Of the 11 patients, 6 patients were male, and 5 patients were female. Average age of patient at the time of surgery was 29.8 years (range : 13 to 50 years). Eight patients had complex partial seizures (CPS), and 3 patients had generalized seizures (GS) prior to surgery. Six patients with CPS and 3 patients with GS had previously undergone epilepsy surgery (left temporal lobectomy in 4 patients, corpus callosotomy in 4 patients, corpus callosotomy with topectomy in 1 patient). Case 2 underwent corpus callosotomy due to band heterotophia. Case 8 who had multiple bilateral epileptic foci underwent corpus callosotomy with topectomy. Mean duration between first epilepsy surgery and VNS implantation was 4.3 years (range : 0.9 to 11.6 years). The remaining 2 patients had severe brain injury. Seizure attacks were seen at an average of 40.3 times/month (range : 1/month to 4/day). Mean follow-up duration after VNS was 22.5 months (range : 6 months to 29 months). Patients' detailed clinical profiles are summarized in Table 1. Mean device parameters during follow-up were as follows : current output, 1.08 mA (range : 0.5-1.75 mA); stimulation frequency, 29 Hz (range : 20-30 Hz); pulse width, 590 μs (range : 500-750 μs); signal on-time, 35.4 sec (30 or 60 sec); signal off-time, 4.4 min (range : 1.8-5 min) (Table 2). Average postoperative seizure frequency was 1/month. Reductions in seizure frequency across time are shown in Table 3. Median seizure frequency at baseline was 40.3 seizures per month. After 6 months of VNS, seizure reduction rate was 74.3%. After 12 months of VNS, seizure reduction rate was 85.2%. After 18 months, seizure reduction rate was 92.4%. After 24 months, seizure reduction rate was 97.2%. Seizure severity was also decreased. Hoarseness occurred in 2 patients, and neck pain occurred in 1 patient during the stimulation. All these adverse events were well tolerated or were controlled by adjustment of output currents. No serious side effects occurred during the operation or follow-up period.

DISCUSSION

VNS is a potential treatment modality for epilepsy patients who are refractory to both medical and surgical

Table 1. Patients' clinical profiles

Case number	Age/Sex	Prior surgery	Seizure frequency (/month)	F/U duration (month)	Semiology
1	29/F	TL, left	45	29	CPS
2	13/M	CC	15	28	CPS
3	25/F	TL, left	60	27	CPS
4	32/M	TL, left	1	27	CPS
5	19/F	CC	5	24	Absence Sz
6	24/M	CC	75	19	Absence Sz
7	50/F	TL, left	3-4	14	CPS
8	29/M	CC	3-4	17	CPS
9	37/M	CC	75	7	Absence Sz
10	21/M	(Trauma)	100	29	CPS
11	49/F	(Trauma)	60	29	CPS

TL : temporal lobectomy, CC : corpus callosotomy, CPS : complex partial seizure, Sz : seizure

Table 2. Mean device parameters during follow-up

Case number	Output current (m/A)	Pulse width (μs)	Frequency (Hz)	On/Off time (sec/min)
1	1.25	750	30	30/5
2	1	500	30	30/5
3	0.75	500	30	30/5
4	1.5	500	30	30/5
5	0.75	500	30	30/5
6	1.75	750	30	30/1.8
7	0.5	500	20	30/5
8	1.25	750	30	60/5
9	1.2	750	30	60/2
10	1.0	500	30	30/5
11	1.0	500	30	30/5

Table 3. Reductions in seizure frequency

Case number	Preoperative seizure frequency	Seizure frequency after VNS			
		After 6 m	After 12 m	After 18 m	After 24 m
1	45/m	2/m	1/m	1/6m	0/m
2	15/m	1/6m	0/m	0/m	0/m
3	60/m	0/m	0/m	0/m	0/m
4	1/m	1/3m	1/3m	1/6m	1/6m
5	5/m	0/m	1/2m	0/m	0/m
6	75/m	30/m	2/m	1/m	1/3m
7	3-4/m	2/m	2/m		
8	3-4/m	3/m	2/m	2/m	2/m
9	75/m	30/m			
10	100/m	1/m	1/6m	0/m	0/m
11	60/m	1/6m	0/m	0/m	0/m

VNS : vagus nerve stimulation, m : month

management. Many authors have reported on the long-term efficacy of VNS[1,8,11,12]. Numerous studies have described its safety and effectiveness[10]. Although our study was characterized by a relatively short follow-up period and a small patient group, 6 patients became seizure-free with medication, and 5 patients showed reduced seizure frequency by more than 50% at last follow-up.

Several studies have demonstrated that the effectiveness of VNS therapy increases with time after implantation and have suggested a cumulative effect of VNS therapy in reducing the frequency of seizures[2,3,6,7]. Some attention has been devoted to tailoring VNS therapy to achieve maximum effectiveness[5]. Morrow et al. demonstrated that the overall effect of VNS on seizure frequency reduction amounted to approximately 30% after 12 months, although 2 patients in their group showed 80% seizure reduction[8]. Ardesch et al. reported that overall reduction in seizure frequency was approximately 50% after 5 years[1]. In the patients studied by Ardesch et al., responders experienced a gradual, statistically significant improvement in seizure reduction over time[1]. The investigators have found that patients were capable of reaching seizure frequency reduction of more than 50%, even after 2 years of VNS. George and Morris reported a significant seizure reduction in the first 3 months after implantation[4,7]. DeGiorgio et al. showed that the efficacy of VNS substantially improved over 1 year, and 20% of subjects sustained a reduction (>75%) in seizures[2]. The most likely cause of their long-term improvement is a cumulative effect of VNS on seizures.

Our patients experienced seizure reduction over time. Efficacy of VNS substantially improved over 2 years, and all subjects who had more than 24 months follow-up duration sustained a reduction (>75%) in seizures. All patients experienced reduced seizure severity. In the study by Ardesch et al., patients reported a reduced seizure severity and reduced post-ictal period. Furthermore, patients reported a better quality of life with the aid of VNS[1].

Because of the limited number of patients and the heterogeneity of underlying etiologies in our study, we could not stratify our patients relative to the seizure type or etiology. Our findings suggest, however, that VNS is an effective treatment modality regardless of the type of seizure, semiology, type of previous epilepsy surgery, or etiology. You et al. showed that VNS tended to be better tolerated and more effective in younger patients[13]. They also found that VNS resulted in a >50% reduction in seizure frequency in 53.6% of the children in their study and a >75% decrease in seizure frequency 6 months after VNS implantation[13]. Our study shows that VNS implantation is also effective in adult patients. The adverse events reported by VNS patients in previous studies, including voice alterations and neck pain during stimulation, also occurred in our patients[7,12]. Most of these side effects, however, were transient or could be controlled by adjusting the current output.

CONCLUSION

Our results suggest that VNS is an effective non-pharmacologic treatment option in patients with surgically refractory epilepsy and in patients with post-traumatic epilepsy due to severe brain injury and that VNS possesses cumulative efficacy with time. However, more cases with longer follow up evaluation will be necessary.

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